[TRANSLATION]

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(71) Applicant: 000008725 Mitsubishi WelPharma Corp. (6-9 Hirano-cho 2-chome, Chuo-ku, Osaka-shi, Osaka-fu)

(72) Inventors: Masakazu FUJIO, Kenji HASHIMOTO, Jiro KATAYAMA, and Atsushi NUMATA (all c/o Welfide Corp., Drug Creation Laboratory, 7-25 Koyada 3-chome, Iruma-shi, Saitama-ken)

(54) [Title of Invention]: 1-AZABICYCLOALKANE COMPOUNDS AND PHARAMACEUTICAL APPLICATIONS FOR THE SAME

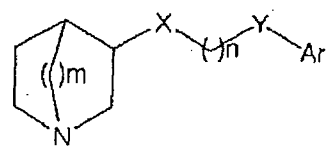
(54) **Abstract:**

[Purpose] To provide a novel compound having the action of effecting α-7 nicotinic receptors or of effecting α-7 nicotinic receptor sections and useful as a therapeutic or preventive agent for Alzheimer disease, cognitive

function disorder, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pain, de la Tourette syndrome, Parkinson's disease, Huntington's disease, etc.

[Solution] 1-Azabicycloalkane compounds represented by the formula (I):

[CHEM. 1]



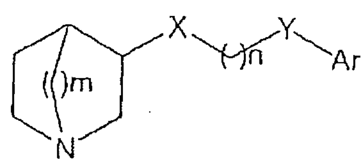
(I)

(wherein respective codes denote as defined in the specification), optical isomers thereof, or pharmaceutically acceptable salts thereof.

[Claims]

[Claim 1] 1-Azabicycloalkane compounds represented by the formula (I):

[CHEM. 1]



(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salts thereof.

[Claim 2] 1-Azabicycloalkane compounds according to Claim 1 wherein the bicyclic aromatic heterocycle is benzothiophene, benzofuran, benzothiazole, or benzoimidazole, optical isomers thereof or pharmaceutically acceptable salts thereof.

[Claim 3] 1-Azabicycloalkane compounds according to Claim 1, which are selected from the following compounds, optical isomers thereof or pharmaceutically acceptable salts thereof:

(1) 3-((Benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane;

(2) (R)-3-((benzo[b]thiophene-2-il)methoxy)-1-azabicylco[2,2,2]octane;

(3) (S)-3-((benzo[b]thiopehne-2-il)methoxy)-1-azabicyclo[2,2,2]octane;

(4) 3-((Benzo[b]thiopehen-3-il)methoxy)-1-azabicyclo[2,2,2]octane;

(5) 3-((2-Naphthyl)methoxy)-1-azabicyclo[2,2,2]octane;

(6) 3-((1-Naphthyl)methoxy)-1-azabicyclo[2,2,2]octane;

(7) 3-(2-(benzo[b]thiopehne-2-il)ethyl)-1-azabicyclo[2,2,2]octane;

(8) (+)-3-(2-(Benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane;

(9) (−)- 3-(2-(Benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane;

(10) 3-(2-(Benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane;

(11) (+)-3-(2-(Benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octane
;

(12) (−)- 3-(2-(Benzo[b]thiophene-2-il)
-2-oxoethyl)-1-azabicyclo[2,2,2]-octane;

(13) 3-(2-(Benzothiazol-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane;

(14) 3-(2-(1-Methylbenzoimidazol-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octan
e;

(15) 3-(2-(Benzo[b]furan-2-il)-2-oxothyl)-1-azabicyclo[2,2,2]octane;

(16) 3-((Benzo[b]thiophene-2-il)methyl)-1-azabicyclo[2,2,2]octane;

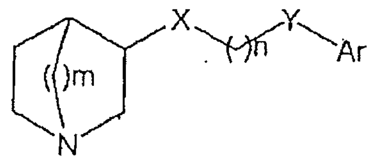
(17) 3-((Benzo[b]thiophene-2-il)carbonyl)-1-azabicyclo[2,2,2]octane;

(18) 3-(3-(Benzo[b]thiophene-2-il)propyl)-1-azabicyclo[2,2,2]octane; and

(19) 3-(3-(Benzo[b]thiophene-2-il)-3-oxopropyl)-1-azabicyclo[2,2,2]octane.

[Claim 4] A ligand of α-7 nicotinic receptors, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 2]

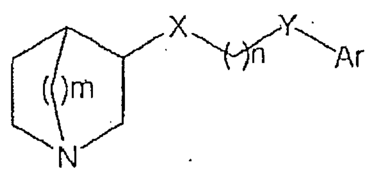


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 5] Medical agents effecting α-7 nicotinic receptors or α-7 nicotinic receptor sections, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 3]

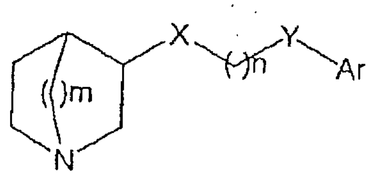


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 6] Medical agent for improving cognitive function disorder, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 4]

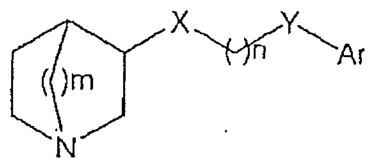


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 7] Medical agents for preventing dementia, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 5]

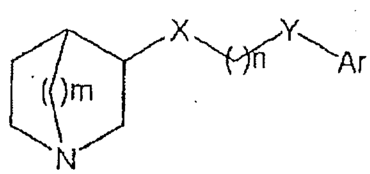


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 8] Therapeutic agents for schizophrenia, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 6]

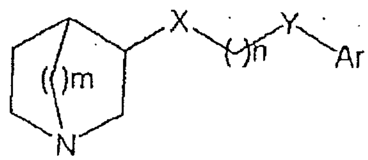


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 9] Medical agents for improving the negative symptoms of schizophrenia, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 7]

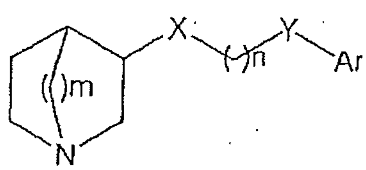


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 10] Therapeutic agents for attention deficit hyperactivity disorder, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 8]

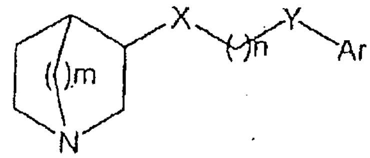


(I)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Claim 11] Therapeutic agents for Alzheimer disease, comprising 1-azabicyclo-alkane compounds represented by the formula (I):

[CHEM. 9]



(1)

(wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salt thereof.

[Detailed Description of The Invention]

[0001]

[Field of the Invention] The present invention relates to novel 1-azabicycloalkane compounds for providing a pharmaceutical useful for diseases in the central nervous system.

[0002]

[Prior Art] Nicotinic receptors are known to be present in a number of the subtypes, at least 11 subtypes having been now identified (α2~9 and β2~4) (general reviews: *Trends in Pharmacological Sciences*, 12: 34-40, 1991; and *Progress in Neurobiology*, 53, 199-237, 1991). It is known that nicotinic receptors are present as pentamers of these subtypes, which form ion channels and uptake calcium ions, etc. into cells. Mainly 2 kinds of the subtypes ($\alpha 4\beta 2$ and $\alpha 7$) are known to be present in brains, and the $\alpha 4\beta 2$ nicotinic receptor is formed as the hetero-oligomer of $\alpha 4$ sub-units and $\beta 2$ sub-units while the $\alpha 7$ nicotinic receptor is formed as the homo-oligomer of $\alpha 7$ sub-units. These subtypes ($\alpha 4\beta 2$ nicotinic receptor and $\alpha 7$ nicotinic receptor) are also broadly distributed in various brain sites (cerebral cortex, hippocampus, etc.). Nicotinic receptors in the central nervous system ($\alpha 4$

$\beta 2$ receptor and $\alpha 7$ nicotinic receptor) are known to be involved in various physiological functions such as the generation and differentiation of nerves, learning and the formation of memories, and rewards (general reviews: *Brain Research Reviews*, 26:198-216, 1998; *Trends in Neurossciences*, 22: 555-561, 1999; *Molecular Neurobiology*, 20:1-16, 1999). Nicotinic receptors present in anterior synapses are known to play critical roles in the discharge of various neurotransmitters (acetylcholine, dopamine, glutamic acid, etc.) (general reviews: *Trends in Pharmacological Sciences*, 20: 92-98, 1997; *Annual Reviews of Neuroscience*, 22: 443-485, 1999 and *Molecular Neurobiology*, 20: 1-16, 1999). Also, nicotinic receptors present in posterior synapses are known to play critical roles in cholinergic nerve conduction (general reviews: *Trends in Pharmacological Sciences*, 22: 555-561, 1999 and *Molecular Neurobiology*, 20: 1-16, 1999).

[0003] On the other hand, the acetylcholine system is one of major nerve conductors in the central nervous system, and is known to be playing critical roles in the regulation of nervous activities of cerebral cortex and hippocampus, while the possibility has been suggested of its involvement in various central diseases. For example, nicotinic receptors ($\alpha 4 \beta 2$ receptor and $\alpha 7$ nicotinic receptor), among acetylcholine-system receptors, in the cerebral cortex and hippocampus are reported to have been decreased in the pathlogic autopsy brains of Alzheimer patients (*Journal of Neurochemistry*, 46: 288-293, 1986; *Alzheimer's Disease Reviews*, 3: 20-27, 1998 and *Alzheimer's Disease Reviews*, 3: 28-34, 1998). In addition, the mRNA content of $\alpha 7$ nicotinic receptor in the lymphocyte of Alzheimer patients is reported to have significantly increased in comparison to the mRNA content of $\alpha 7$ nicotinic receptor in the lymphocyte of normal people (*Alzheimer's Disease Reviews*, 3: 29-36, 1997). Also, the mRNA content of

$\alpha 7$ nicotinic receptor in the hippocampus of Alzheimer patients is reported to have significantly increased in comparison to the mRNA content of $\alpha 7$ nicotinic receptor in the hippocampus of normal people (*Molecular Brain Research*, 66: 94-103, 1999). Based on the absence of recognizably different mRNA contents of other subtypes ($\alpha 3$ and $\alpha 4$) in brains between normal people and Alzheimer patients, this report suggests that $\alpha 7$ nicotinic receptors play a critical role in Alzheimer disease conditions. In an experiment using the primary culture of rat cerebral cortex, nicotine has been reported to show the effect of nerve protection via $\alpha 7$ nicotinic receptors from neurotoxin of amiloyd β peptide (*Annuals of Neurology*, 42: 159-16, 1997). A theory of oxidation stress due to radical reaction has been proposed as one of mechanisms for the neurotoxin of amiloyd β peptide, suggesting that the irritation of nicotinic receptors could be regulating intracellular oxidation stress. Accordingly, $\alpha 7$ nicotinic receptors are believably highly related to the cause of, or the action sites of a therapeutic agent for Alzheimer disease.

[0004] Further on the other hand, relationship between schizophrenia patients and $\alpha 7$ nicotinic receptors has been attracting attentions (general reviews: *Harvard Reviews of Psychiatry*, 2: 179-192, 1994; *Schizophrenia Bulletin*, 22: 431-445, 1996; *Schizophrenia Bulletin*,24: 189-202, 1998 and *Trends in Neurosciences*, 22: 555-561, 1999). Also, the number of $\alpha 7$ nicotinic receptors in the pathlogic autopsy brains (cerebral cortex and hippocampus) of schizophrenia patients is reported to have been decreased (*Schizophrenia Bulletin*, 22: 431-445, 1996; *Schizophrenia Bulletin*,24: 189-202, 1998 and *NeuroReport*, 10: 1779-1782, 1999). Also reported are that the abnormality of sensory gating observed with schizophrenia patients can be improved by the administration of nicotine and that $\alpha 7$

nicotinic receptors are involved in this phenomenon. Accordingly, $\alpha 7$ nicotinic receptors are believably highly related to the cause of schizophrenia. Incidentally, the mechanism of schizophrenia conditions has not been clarified by now, but a hypothetical theory has been widely proposed that it is related with the declined neurotransmission system of glutamic acid, one of excitatory amino acids (general reviews: *Harvard Reviews of Psychiatry*, 3: 241-253, 1996; *American Journal of Psychiatry*, 148: 1301-1308, 1991 and *Archives of General Psychiatry*, 52: 998-1007, 1995). Agents effecting $\alpha 7$ nicotinic receptors are believably to activate the declined neurotransmission system of glutamic acid by discharging glutamic acid from anterior synapses, and thereby to improve symptoms (positive and negative symptoms, cognitive function disorder, etc.) of schizophrenia. In such manners, $\alpha 7$ nicotinic receptors are believably highly related to the action sites of a therapeutic agent for schizophrenia.

[0005] Furthermore, since $\alpha 7$ nicotinic receptors are present in a reward system which is believably related to smoking dependence, agents effecting $\alpha 7$ nicotinic receptors are also possibly related to the suppression of smoking (*Trends in Neurosciences*, 22: 555-561, 1999; *NeuroReport*, 10: 697-702, 1999 and *Neurosciences*, 85: 1005-1009, 1998). Thus, agents effecting $\alpha 7$ nicotinic receptors or agents effecting $\alpha 7$ nicotinic receptor sections are believably useful as therapeutic or preventive agents for Alzheimer disease, cognitive function disorder, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pain, de la Tourette syndrome, Parkinson's disease, Huntington's disease, etc., and have some advantages in comparison to compounds as the agent of effecting $\alpha 4 \beta 2$ nicotinic receptors. Accordingly, those agents selectively effecting $\alpha 7$ nicotinic receptors or sections thereof are desirable. Also,

because of their effect of nervous protection, the present agents are useful for the therapy or prevention of nervous degeneration diseases with the disorder of cholinergic neurotransmission. Moreover, the agents can be used for promoting the inhibition of smoking.

[0006] Known as an earlier developed agent of effecting α7 nicotinic receptor sections is 3-[(2,4-Dimethoxy)benzylidene]anabasein [sic] (developmental code number GTS-21: WO94/05288), and spiro[1-azabicyclo[2,2,2]octane-3,5'-oxazolidine-2'-on] is known as an earlier developed agent of effecting α7 nicotinic receptors (developmental code number AR-R17779: WO96/06098), but either of these agents is known to have poor compatibility with α7 nicotinic receptors, and problems such as low cerebral transition, etc. WO97/30998 also discloses compounds azabicyclo carbamate compounds as agonists of α7 nAChR (α7 nicotine acetylcholine receptor), but the compatibility of these compounds to the receptors is not strong. In addition, known compounds structurally similar to compounds according to the present invention include 1-azacycloalkane compounds having compatibility with muscaline receptors (Japanese Laid-Open Patent Application Hei-04 (1992)-226981A), azabicyclo compounds as calcium channel antagonists (Japanese Publication of International Patent Application Hei-07 (1995)-503463), quinacridone derivatives as squalene synthetase inhibitors (Japanese Publications of International Patent Applications Hei-08 (1996)-500098 and Hei-08 (1996)-504803), 3-(2-oxo-2-phenylethyl) quinuclidine and 3-(2-phenylethyl) quinuclidine (Khim. Geterotsikl. Soedin, [1983], 3: 381-385 (Chemical Abstract, 100: 22563w)), etc. However, none of them are intended as agents of effecting α7 nicotinic receptors.

[0007]

[Problems to be Solved by Invention] The object of the present invention is to provide novel compounds having the powerful action of effecting α-7 nicotinic receptors or effecting α-7 nicotinic receptor sections and useful as therapeutic or preventive agents for Alzheimer disease, cognitive function disorder, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pain, de la Tourette syndrome, Parkinson's disease, Huntington's disease, etc., therapeutic or preventive agents for nervous degeneration diseases with the disorder of cholinergic neurotransmission, and moreover, agents for promoting the inhibition of smoking.

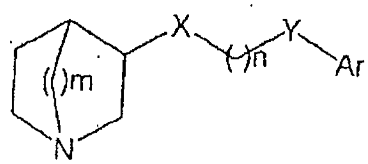
[0008]

[Means as Solution to Problems] As a result of intensive exploration, the present inventors have found that 1-azabicycloalkane compounds represented by the formula (I), optically active compounds thereof or pharmaceutically acceptable salts thereof have selective and powerful compatibility with α-7 nicotinic receptors, particularly the selective and powerful action of effecting α-7 nicotinic receptors or of effecting α-7 nicotinic receptor sections. Accordingly, compounds according to the present invention can become useful as therapeutic or preventive agents for Alzheimer disease, cognitive function disorder, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pain, de la Tourette syndrome, Parkinson's disease, Huntington's disease, etc., therapeutic or preventive agents for nervous degeneration diseases with the disorder of cholinergic neurotransmission, and moreover, agents for promoting the inhibition of smoking. The present invention may be stated as follows:

1. 1-Azabicycloalkane compounds represented by the formula (I):

[0009]

[CHEM. 10]



(I)

[0010] (wherein X is either absent or denotes O, S or NH; Y denotes CH_2 or C=O; m denotes 1 or 2; n denotes 0 or an integer of 1~3; Ar denotes an optionally substituted bicyclic aromatic heterocycle or an optionally substituted napthyl group), optical isomers thereof, or pharmaceutically acceptable salts thereof.

2. 1-Azabicycloalkane compounds as defined in the above statement 1, wherein the bicyclic aromatic heterocycle is benzothiophene, benzofuran, benzothiazole, or benzoimidazole, optical isomers thereof or pharmaceutically acceptable salts thereof.

[0011] 3. 1-Azabicycloalkane compounds as defined in the above statement 1, which are selected from the following compounds, optical isomers thereof or pharmaceutically acceptable salts thereof:

(1) 3-((Benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane;

(2) (R)-3-((benzo[b]thiophene-2-il)methoxy)-1-azabicylco[2,2,2]octane;

(3) (S)-3-((benzo[b]thiopehne-2-il)methoxy)-1-azabicyclo[2,2,2]octane;

(4) 3-((Benzo[b]thiopehen-3-il)methoxy)-1-azabicyclo[2,2,2]octane;

(5) 3-((2-Naphthyl)methoxy)-1-azabicyclo[2,2,2]octane;

(6) 3-((1-Naphthyl)methoxy)-1-azabicyclo[2,2,2]octane;

(7) 3-(2-(benzo[b]thiopehne-2-il)ethyl)-1-azabicyclo[2,2,2]octane;

(8) (+)-3-(2-(Benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane;

(9) (−)- 3-(2-(Benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane;

(10) 3-(2-(Benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane;

(11) (+)-3-(2-(Benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octane ;

(12) (−)- 3-(2-(Benzo[b]thiophene-2-il) -2-oxoethyl)-1-azabicyclo[2,2,2]-octane;

(13) 3-(2-(Benzothiazol-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane;

(14) 3-(2-(1-Methylbenzoimidazol-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octane;

(15) 3-(2-(Benzo[b]furan-2-il)-2-oxothyl)-1-azabicyclo[2,2,2]octane;

(16) 3-((Benzo[b]thiophene-2-il)methyl)-1-azabicyclo[2,2,2]octane;

(17) 3-((Benzo[b]thiophene-2-il)carbonyl)-1-azabicyclo[2,2,2]octane;

(18) 3-(3-(Benzo[b]thiophene-2-il)propyl)-1-azabicyclo[2,2,2]octane; and

(19) 3-(3-(Benzo[b]thiophene-2-il)-3-oxopropyl)-1-azabicyclo[2,2,2]octane.

[0012] 4. A ligand of α-7 nicotinic receptors, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

5. Medical agents effecting α-7 nicotinic receptors or α-7 nicotinic receptor sections, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

6. Medical agent for improving cognitive function disorder, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

7. Medical agents for preventing dementia, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

8. Therapeutic agents for schizophrenia, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

9. Medical agents for improving the negative symptoms of schizophrenia, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

10. Therapeutic agents for attention deficit hyperactivity disorder, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

11. Therapeutic agents for Alzheimer disease, comprising 1-azabicyclo-alkane compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof.

[0013]

[Mode of Working Invention] Specific examples of respective groups in the formula (I) include the following: A bicyclic aromatic heteroring of Ar means a structure of having an aromatic heteroring and a benzene ring, or same or different aromatic heterorings, jointly sharing a mutual part of the rings and being condensed, and its examples may include benzoxazole, benzothiazole, 1,2-benzisoxazole, 1,2-benzisothiazole, indole, 1-benzofuran, 1-benzothiophene, quinoline, isoquinoline, quinazoline, etc. Also, Ar can be bonded with Y from any of carbon atoms on the ring.

[0014] A substitution group in the bicyclic aromatic heteroring may include (1) halogen selected from fluorine, chlorine, bromine and iodine, (2) alkyl having 1~4 carbon atoms selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, etc., (3) alkoxy constituted of alkyl having 1~4 carbon atoms and oxygen atom, which is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tertiary butoxy, etc., (4) haloalkyl

having 1~4 carbon atoms, selected from fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, etc., (5) hydroxy, (6) amino, (7) dialkylamino respectively and independently having alkyl having 1~4 carbon atoms, which is selected from dimethylamino, diethylamino, N-methyl-N-ethylamino, pyrolidine-1-il, etc., the alkyl section of which is optionally forming a ring, (9) nitro, (10) cyano, (10) acyl constituted from alkyl having 1~4 carbon atoms and carbonyl, which is selected from formyl, acetyl, propionyl, 2-methylpropionyl, butyryl, etc. (11) carboxylic acid, (12) ester constituted from alkoxy having 1~4 carbon atoms and carbonyl, which is selected from methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tertiary butoxycarbonyl, etc., (13) carbamoyl, (14) N-alkylcarbamoyl or N,N-dialkylcarbamoyl constituted of monoalkylamino or dialkylamino and carbonyl, (15) acylamino or diacylamino constituted from acyl (as defined above) and amino, (16) thiol, (17) alkylthio constituted of alkyl having 1~4 carbon atoms and sulfur atom, selected from methylthio, ethylthio, propylthio, butylthio, etc., (18) alkoxycarbonylamino constituted of ester and amino, (19) sulfamoyl, (20) N-alkylsulfamoyl or N,N-dialkylsulfamoyl constituted of monoalkylamino or dialkylamino and sulfone, etc., and any of carbon atoms in Ar may be have one or more, preferably 1~3 substitution groups. When same or different substitution groups as described above are present on adjacent carbon atoms in Ar, adjacent substitution groups may be jointly forming a new ring with each other.

[0015] Preferable compounds represented by the formula (I) are as follows, numbers denoting example numbers:

(1) 3-((benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane; (2) ®-3-((benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane; (3) (S)-3-((benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane; (5) 3-((2-naphthyl)methoxy)-1-azabicyclo[2,2,2]octane; (7) 3-(2-(benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane; (8) (+)-3-(2-(benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane; (9) (−)-3-(2-(benzo[b]thiopehen-2-il)ethyl)-1-azabicyclo[2,2,2]octane; (10) 3-(2-(benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane; (11) (+)-3-(2-(benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane; (12) (−)-3-(2-(benzo[b]thiopehen-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane; (13) 3-(2-(benzothiaxol-2-il)-2-ocoethyl)-1-azabicyclo[2,2,2]octane; and (15) 3-(2-(benzo[b]furan-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane.

[0016] Compounds represented by the formula and pharmaceutically acceptable salts thereof may include acid addition salts with inorganic acids (such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, etc.) or organic acids (such as acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, maleic acid, fumaric acid, methane sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, camphor sulfonic acid, ascorbic acid, etc.). For the purpose of crystallization, the compound may be also made to oxalate. Since compounds represented by the formula (I) and hydrates or pharmaceutically acceptable slats thereof may sometimes present in the form of hydrate or solvate, these hydrates (1/2 hydrate, 1/3 hydrate, monohydrate, 3/2 hydrate, dihydrate, trihydrate, etc.) and solvates are also covered within the scope of the present invention. When a compound represented by the formula (I) has a symmetric atom, at least 2 kinds of

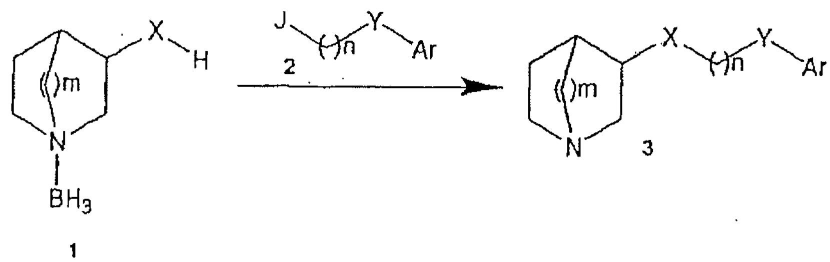
optical isomers are present. These optical isomers and lacemic bodies thereof are also covered within the scope of the present invention.

[0017] Compounds according to the present invention and represented by the formula (I) can be synthesized according to the following processes, while respective codes used in reaction schemes denote the same as defined above unless otherwise defined:

Synthetic Process 1

[0018]

[CHEM 11]



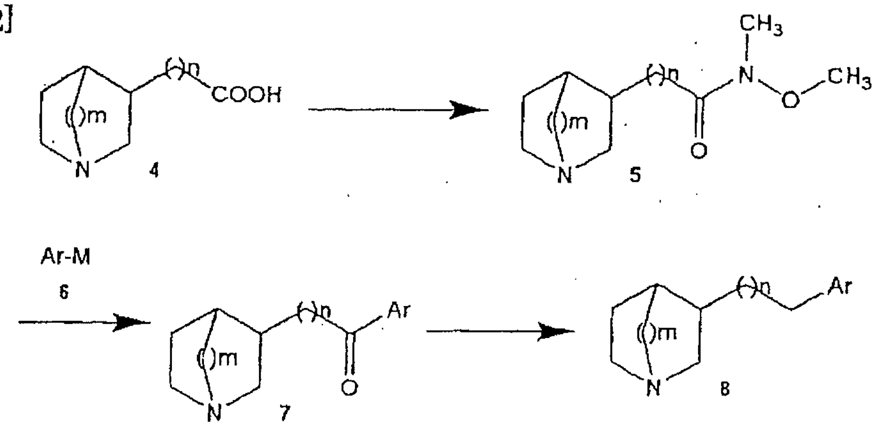
[0019] A compound represented by the formula (3) can be obtained by the reaction of a compound represented by the formula (1) with a compound represented by the formula (2) (wherein J denotes an appropriate leaving group generally used in organic synthesis chemistry such as chlorine atom, bromine atom, iodine atom, trifluoromethane sulfonyloxy, p-toluene sulfonyloxy, methane sulfonyloxy, etc.) in the presence of an appropriate base generally used in organic synthesis chemistry such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium tertiary butoxide, sodium, potassium, potassium carbonate, potassium hydrogen carbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, sodium hydride, butyl lithium, etc., in an appropriate solvent not inhibiting the reaction (such as benzene, toluene, xylene, dimethyl formamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, mixture thereof, etc.), at a temperature from room temperature to the refluxing temperature of the solvent, for 0.1~48 hours, and by subsequent

boron deprotection using an appropriate acid generally used in organic synthesis chemistry such as dilute hydrochloric acid, dilute sulfuric acid, etc.

Synthetic Process 2

[0020]

[CHEM 12]



[0021] A compound represented by the formula (5) can be obtained by the reaction of a compound represented by the formula (4) with O-dimethyl hydroxyl amine in an appropriate solvent not inhibiting the reaction (such as benzene, toluene, xylene, ethyl acetate, dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, methylene chloride, chloroform, ethylene dichloride, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, mixture thereof, etc.), in the presence of an appropriate base not inhibiting the reaction (such as triethyl amine, pyridine, dimethyl aminopyridine, diisopropyl ethyl amine, potassium carbonate, potassium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, etc.), upon the addition of an appropriate condensation agent (such as diethyl cyanophosphate, benzotriazole-1-iloxy-tris(dimethylamino) phosphonium hexafluorophsophate (Bop reagent), 1-ethyl-3-(3'-dimethyl aminopropyl) carbodiimide (WSCI), 1,3-dicyclohexyl carbodiimide (DCCD),

etc.) at a temperature from −78℃ to the refluxing temperature of the solvent, and for 0.1~48 hours. A compound represented by the formula (5) can be also obtained from a compound represented by the formula (4) in an appropriate solvent not inhibiting the reaction (such as benzene, toluene, xylene, ethyl acetate, dimethyl sulfoamide, dimethyl acetamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, methylene chloride, chloroform, ethylene dichloride, mixture thereof, etc.) in the presence of an appropriate base not inhibiting the reaction (such as triethyl amine, pyridine, dimethyl aminopyridine, diisopropyl ethyl amine, potassium carbonate, potassium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, etc.), by reaction at a temperature from 0℃ to the refluxing temperature of the solvent, for 0.1~48 hours, upon the addition of N,O-dimethyl hydroxyl amine to mixed acid anhydrides formed by the addition of an appropriate acid chloride (such as pivaloyl chloride, isobutyl chlorocarbonate, ethyl chlorocarbonate, etc.) at a temperature from −20℃ to 10℃. Furthermore, a compound represented by the formula (5) can be also obtained by the reaction of a compound represented by the formula (4) with an appropriate halogenation agent (such as phosphorous oxychloride, phosphorous pentachloride, thionyl chloride, phosphorous tribromide, phosphorous pentabromide, thionyl bromide, etc.) or 1,1'-carbonylbis-1H-imidazole or the like, to obtain a reactive intermediate, and the subsequent reaction of the reactive intermediate with N,O-dimethyl hydroxyl amine.

[0022] A compound represented by the formula (7) can be obtained by the reaction of a compound represented by the formula (6) (wherein M denotes a metal such as lithium, magnesium chloride, magnesium bromide, etc.) with a compound represented by the formula (5) in a solvent not inhibiting

the reaction (such as diethyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxan, a mixed solvent thereof, etc.) at a temperature from −78℃ to the refluxing temperature of the solvent, and for 0.1~24 hours. A compound represented by the formula (8) can be obtained by the reaction of a compound represented by the formula (7) in trifluoroacetic acid, with the addition of triethyl silane, at a temperature from 0℃ to the refluxing temperature of the solvent, and for 0.1~24 hours. A compound represented by the formula (8) can be also obtained from a compound represented by the formula (7) by once forming an alcoholate with the use of an appropriate reducing agent, such as sodium boron hydride, aluminum lithium hydride, diisobutyl aluminum hydride, etc., then dissolving the alcoholate in acetonitrile, and causing reaction at a temperature from 0℃ to the refluxing temperature of the solvent, for 0.1~24 hours upon the addition of sodium iodide and chlorotrimethyl silane.

[0023] A compound according to the present invention thus obtained can be isolated and purified by means of conventional methods such as recrystallization, column chromatography, etc. When the product is obtained as a racemic body, a desired optically active substance can be obtained by splitting, for example, by means of the fractional recrystallization of optically active acid and salt, or by passing through a column filled with an optically active carrier. Respective diasteromers can be isolated by means of fractional crystallization, chromatography, etc. These can be also obtained by using optically active compounds as the starting materials. Stereoisomers can be also isolated by means of recrystallization, column chromatography, etc.

[0024] When a 1-azabicycloalkane compound according to the present invention, optical isomer thereof or a pharmaceutically acceptable salt

thereof, is used as a pharmaceutical, it can be orally or non-orally administered in the form of pharmaceutical compositions or preparations (such as tablets, pills, capsules, granules, powder, syrup, emulsion, elixir, suspension, solution, injection, instillation, suppositories, etc.) obtained by blending the compound according to the present invention with a carrier acceptable in preparation (such as fillers, binders, disintegrators, taste modifiers, flavor modifiers, emulsifiers, diluents, solution additives, etc.). Pharmaceutical compositions can be prepared according to a conventional method. In the present patent specification, a term: non-oral administration is used to include subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, instillation, etc. Preparations for injection, for example, aqueous or oil suspensions for aseptic injection, can be prepared according to known methods in the art, using an appropriate dispersion agent, wetting agent or suspension agent. The preparations for antiseptic injection may be also, for example, antiseptic injectionable solutions or suspensions in a non-toxic diluent or solvent which is non-toxic and can be non-orally administered, such as aqueous solutions, etc. Usable vehicles or acceptable solvents may include water, Ringer's solution, isotonic salt solution, etc. In addition, antiseptic non-volatile oils can be usually used as a solvent or suspending solvent, too. For this purpose, any non-volatile oils and fatty acids can be used, including natural, synthetic or semi-synthetic fatty oils or fatty acids, and natural, synthetic or semi-synthetic mono-, di- or tri-glycerides, as well.

[0025] Suppositories for direct administration into large intestine can be manufactured by blending the medical component with an appropriate, non-irritating, solid base, for example, cocoa butter or polyethylene glycols, which remains solid at room temperature but becomes liquid at intestine

temperatures and intrarectally melts to release the medical component. Solid administration preparations for oral administration may include powder, granules, tablets, pills, capsules, etc. as above described. In such types of preparations, active component compounds can be blended with at least one of additives, for example, sugar, lactose, cellulose sugar, mannitol, maltitol, dextran, starches, agar, alginates, chitins, chitosans, pectins, trangacanth gums, gums Arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. Such types of preparations can also contain further additives as usual, for example, including inert diluents, lubricants such as magnesium stearate, etc., preservatives such as Parabens, sorbins, etc., anti-oxidants such as ascrobic acid, α-tocopherol, cystein, etc., disintegrators, binders, thickeners, buffer agents, sweeteners, flavoring agents, perfume agents, etc. Tablets and pills can be also manufactured further with enteric coating. Liquid preparations for oral administration include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, solutions, etc., and these preparations may also contain an inert diluent usually used in the art, for example, water.

[0026] Compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof have selective and powerful actions of effecting α-7 nicotinic receptors or the action of effecting α-7 nicotinic receptor sections and can be useful as therapeutic or preventive agents for Alzheimer disease, cognitive function disorder, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pains, de la Tourette syndrome, Parkinson's disease, Huntington's disease, etc., as therapeutic or preventive agents for nervous degeneration diseases with the disorder of cholinergic neurotransmission, and moreover, as agents for promoting the inhibition of smoking. The amount to be administered can be

determined depending upon the ages, weight, general health conditions, sex and foods of a patient, the timing and method of administration, excretion rates, drug combinations, disease conditions of the patient at the time of treatment, in consideration of these and other factors. Compounds according to the present invention, optical isomers thereof or pharmaceutically acceptable salts thereof have low toxicity and can be used safely, and the daily dosage may be different depending upon the conditions and weight of a patient, the kind of compounds, the administration route, etc., but a desirable daily dosage may be, for example, when administered non-orally by subcutaneous injection, intravenous injection, intramuscular injection or intraperitoneal injection, about 0.01~50mg/man/day, preferably 0.01~20mg/man/day, and when orally administered, about 0.01~150mg/man/day, preferably 0.01~100mg/man/day. Also, compounds according to the present invention, which have selective and powerful compatibility with α-7 nicotinic receptors, are useful, as ligands for α-7 nicotinic receptors, for application as labelled compounds for intracerebral α-7 nicotinic receptors, etc.

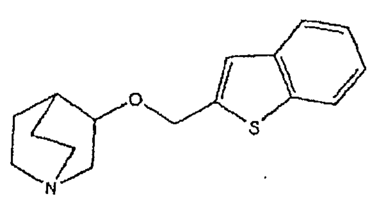
[0027]

[Examples] In the following, the present invention shall be further explained in detail by referring to illustrative examples, preparation formula examples and experimental examples, but the present invention should not be subject to any restriction by these examples.

[Example 1]

[0028]

[CHEM. 13]

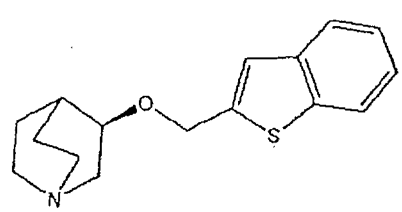


[0029] Into 5 mL of dimethyl formamide, 0.5gr of 1-azabicyclo[2,2,2]octane-3-ol-boran complex was dissolved, and upon the addition of 0.17gr of sodium hydride (60%) under iced cooling, the solution was stirred for 30 minutes. Into the reaction liquid, 0.77gr of 2-chloromethylbenzo[b]-thiophene was added, and the stirring was continued further for an hour. After the reaction was completed, the reaction liquid was poured into iced water, extracted with ethyl acetate and dried over sodium sulfate. A residue obtained by solvent condensation was subjected to silica gel chromatography, and the (hexane : ethyl acetate = 9 : 1) effluent was condensed to obtain 0.3gr of 3-((benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane-boran complex. This compound was dissolved in 10mL of acetone, and upon the addition of 3N hydrochloric acid under iced cooling, the solution was stirred at room temperature for an hour. After the reaction was completed, water was added to the residue obtained by solvent condensation, and the product was extracted with ethyl acetate and dried over sodium sulfate. The residue obtained by solvent condensation was dissolved in ethyl acetate, and crystals deposited upon the addition of hydrochloric acid-ether were recovered by filtration to obtain 0.17gr of 3-((benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane hydrochloride- 1/2 hydrate. Melting point: 201~203℃.

Example 2

[0030]

[CHEM. 14]

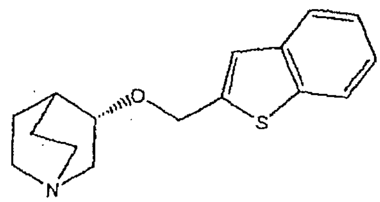


[0031] Using 0.065gr of (R)-1-azabicyclo[2,2,2]octane-3-ol-boran complex, similar reactions as in Example 1 were conducted to obtain 0.021gr of (R)-3-(benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane hydro-chloride. Melting point: 211~212℃; [α]D = −52° (c=0.23. MeOH).

Example 3

[0032]

[CHEM. 15]

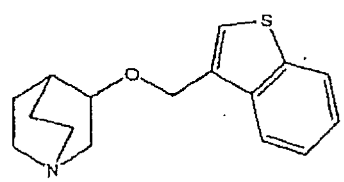


[0033] Using 0.37gr of (S)-1-azabicyclo[2,2,2]octane-3-ol-boran complex, similar reactions as in Example 1 were conducted to obtain 0.061gr of (S)-3-(benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane hydro-chloride. Melting point: 211~213℃; [α]D =+56° (c=0.25. MeOH).

Example 4

[0034]

[CHEM. 16]

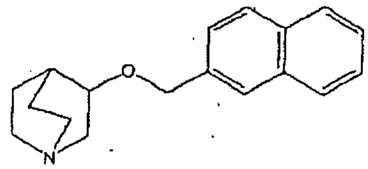


[0035] Using 0.77gr of 3-chloromethylbenzo[b]thiophene, similar reactions as in Example 1 were conducted to obtain 0.155gr of 3-(benzo[b]thiophene-2-il)methoxy)-1-azabicyclo[2,2,2]octane hydrochloride-3/2hydrate. Melting point: 153~156℃.

Example 5

[0036]

[CHEM. 17]

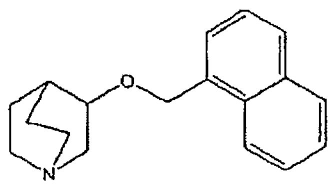


[0037] Using 0.74gr of 2-chloromethylnaphthalnee, similar reactions as in Example 1 were conducted to obtain 0.103gr of 3-((2-naphthyl)methoxy)-1-azabicyclo[2,2,2]octane hydrochloride-monohydrate. Melting point: 187~189℃.

Example 6

[0038]

[CHEM. 18]

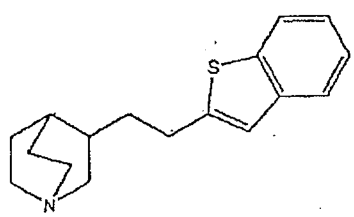


[0039] Using 0.74gr of 1-chloromethylnaphthalnee, similar reactions as in Example 1 were conducted to obtain 0.1gr of 3-((1-naphthyl)methoxy)-1-azabicyclo[2,2,2]octane hydrochloride. Melting point: 191~194℃.

Example 7

[0040]

[CHEM. 19]



[0041] Into 10mL of trifluoroacetic acid, 1.2gr of 3-(2-benzo[b]thiopehne-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane was dissolved, and upon the addition of 1.7mL of triethyl silane, the solution was stirred for 5 days at room temperature. The reaction system was

diluted with 30Lof water and was made alkaline with sodium carbonate, and the intended product was 3 times extracted with chloroform. The organic layer was dried over sodium sulfate, the residue obtained by condensation was subjected to silica gel column chromatography, and the (hexane : ethyl acetate = 7 : 3 ~ 6 : 4) effluent was condensed. The residue was dissolved in acetone, was adjusted with hydrochloric salt with the addition of 32% hydrochloric acid methanol, solvent was distilled off under vacuum, and crystals precipitated upon the addition of isopropanol were recovered by filtration to obtain 0.15gr of 3-(2-(benzo[b]thiophene-2-il)ethyl)-1-azabicyclo[2,2,2]octane-hydrochloride 1/4 hydrate. Melting point: 218~220℃.

[0042] Example 8

Into 10mL of methanol, 0.28gr of (+)-3-(2-(benzo[b]thiopehen-2-il)-2-oxoetyl)-1-azabicyclo[2,2,2]octane was dissolved, and upon the addition of 0.038gr of sodium borate hydride under iced cooling, the solution was stirred at room temperature. After the reaction was completed, the saturated aqueous solution of sodium carbonate was added, and the product was twice extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the residue obtained by the vacuum distillation of solvent was subjected to silica gel chromatography to obtain 0.13gr of alcoholate. Into 5mL of acetonitrile, 0.4gr of sodium iodide was dissolved, and upon the addition of 0.34mL of chlorotrimethyl silane under iced cooling, the solution was stirred for 30 minutes at room temperature. Into a yellow liquid suspension thus formed, 0.13gr of the alcoholate was added, and the mixture was stirred for 30 minutes at room temperature. After the reaction was completed, an aqueous solution of sodium sulfite was added to the reaction product, which

was then made alkaline with the saturated aqueous solution of sodium carbonate. The product was twice extracted with chloroform, the organic layer was dried over anhydrous sodium sulfate and the solvent was removed by vacuum distillation, the residue obtained was subjected to silica gel chromatography to obtain an oily product. The oily product was dissolved in isopropanol, and with the addition of 32% hydrochloric acid-methanol, crystals formed was recovered by filtration to obtain 0.060gr of (+)-3-(2-(benzo[b]thiphene-2-il)ethyl)-1-azabicyclo[2,2,2]octane hydrochloride-1/4 hydrate. Melting point: 248~ 250℃; $[\alpha]_D$ =+41.2° (c=0.25. MeOH).

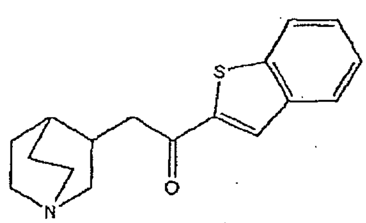
[0043] Example 9

Using 0.31gr of (−)-3-(2-(benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo-[2,2,2]octane, similar reactions as in Example 8 were conducted to obtain 0.015gr of (−)-3-(2-(benzo[b]thiophene-2-il)-ethyl)-1-azabicyclo[2,2,2]-octane hydrochloride. Melting point: 228~232℃; $[\alpha]_D$ =−36.4° (c=0.25. MeOH).

Example 10

[0044]

[CHEM. 20]



[0045] Into 10mL of tetrahydrofuran, 0.76gr of benzo[b]thiophene was dissolved, and upon the addition of 3.5mL of the 1.6N n-butyl lithium solution in hexane under nitrogen atmosphere at −78℃, the solution was stirred for 10 minutes. Into this solution, 5mL of a tetrahydrofuran solution containing 1.0gr of N-methyl-N-methoxy-2-(1-azabicyclo[2,2,2]-octane-3-il)

acetamide was dropped, and the solution was stirred at −78℃ for 15 minutes. After the reaction was completed, the reaction cocktail was twice extracted with chloroform with the addition of water. The organic layer was dried over sodium sulfate, the residue obtained by solvent concentration was subjected to silica gel chromatography and the concentration of chloroform effluent to obtain an oily product. The oily product was dissolved in isopropanol, and upon the addition of 32% hydrochloric acid-methanol, precipitated crystals were recovered by filtration to obtain 0.23gr of 3-(2-benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane hydrochloride. Melting point: 247~249℃.

[0046] Example 11

Into 30mL of a warm ethanol solution containing 2.9gr of 3-(2-(benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane, 20mL of a warm ethanol solution containing 1.3gr of L-malic acid was added. The solution was cooled to room temperature, and crystals precipitated were recovered by filtration. Three and half (3.5) grams of the crystals obtained were thrice recrystallized using water to obtain 0.72gr of (+)-3-(2-enzo[b]thiopehen-2-il)-2-oxoetyl)-1-azabicyclo[2,2,2]octane L-malate. The saturated aqueous solution of sodium carbonate was added to the malate obtained, the intended product was twice extracted with chloroform, the organic layer was dried over anhydrous sodium sulfate, crystals obtained upon solvent condensation were dissolved in methanol, and crystals precipitated upon the addition of hydrochloric acid-methanol were recovered by filtration to obtain 0.28gr of (+)-3-(2-(benzo[b]thiphene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane hydrochloride-1/5 hydrate. Melting point: 226~ 227℃; $[\alpha]_D = -36.2°$ (c=0.25. MeOH).

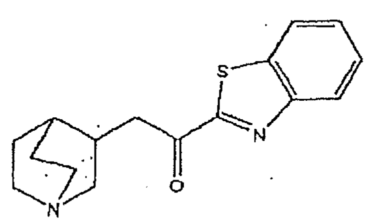
[0047] Example 12

The filtrates formed in Example 11 were blended, and solvents were removed by vacuum distillation. The saturate aqueous solution of sodium carbonate was added to the residue obtained, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and to 10mLof a warm ethanol solution containing 1.15gr of a residue obtained upon solvent concentration, 5mL of a warm ethanol solution containing 0.54gr of D-malic acid was added, and crystals precipitated were recovered by filtration. Crystals thus obtained were thrice recrystallized using ethanol-water to obtain (−)-3-(2-(benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane-D-malate. The saturated aqueous solution of sodium carbonate was added to the malate obtained, the intended product was twice extracted with chloroform, the organic layer was dried over anhydrous sodium sulfate, crystals obtained upon solvent concentration were dissolved in methanol, and crystals precipitated upon the addition of hydrochloric acid-methanol were recovered by filtration to obtain 0.28gr of (−)-3-(2-(benzo[b]thiophene-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]octane hydrochloride. Melting point: 230~ 232℃; $[\alpha]_D = -36.0°$ (c=0.25. MeOH).

Example 13

[0048]

[CHEM. 21]



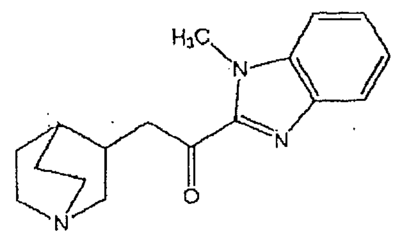
[0049] Using 2.23gr of benzothiazole and 1.0gr of N-methyl-N-methoxy-2-(1-azabicyclo-[2,2,2]octane-3-il)acetamide, similar

reactions as in Example 10 were conducted to obtain 0.24gr of 3-(2-(benzothiazole-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octane hydrochloride. Melting point: 274~275℃.

Example 14

[0050]

[CHEM. 22]

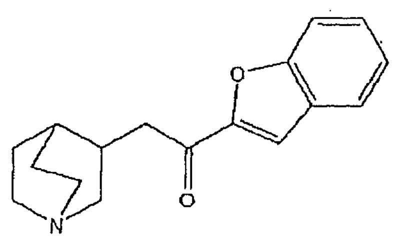


[0051] Using 2.2gr of 1-methyl benzimidazole and 1.0gr of N-methyl-N-methoxy-2-(1-azabicyclo-[2,2,2]octane-3-il)acetamide, similar reactions as in Example 10 were conducted to obtain 0.6gr of 3-(2-(1-methyl benzothiazole-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octane trihydrochloride. Melting point: 246~247℃.

Example 15

[0052]

[CHEM. 23]

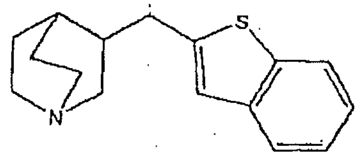


[0053] Using 1.95gr of benzo[b]furan and 1.0gr of N-methyl-N-methoxy-2-(1-azabicyclo-[2,2,2]octane-3-il)acetamide, similar reactions as in Example 10 were conducted to obtain 0.6gr of 3-(2-(benzo[b]furan-2-il)-2-oxoethyl)-1-azabicyclo[2,2,2]-octane hydrochloride-1/5hydrate. Melting point: 288~290℃.

Example 16

[0054]

[CHEM. 24]

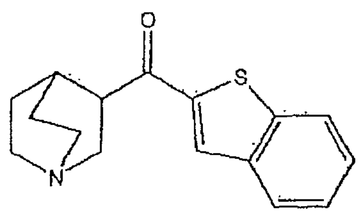


[0055] Using 1.0gr of 3-((benzo[b]thiophene-2-il)carbonyl)-1-azabicyclo-[2,2,2]octane, similar reactions as in Example 8 were conducted to obtain 3-((benzo[b]thiophene-2-il)-methyl)-1-azabicyclo[2,2,2]-octane hydrochloride. Melting point: 264~265℃.

Example 17

[0056]

[CHEM. 25]

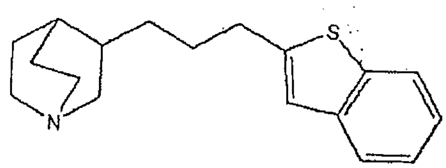


[0057] Using 5.4gr of benzothiophene and 2.0gr of N-methyl-N-methoxy-2-(1-azabicyclo-[2,2,2]octane-3-il)carboxamide, similar reactions as in Example 10 were conducted to obtain 1.0gr of 3-((benzo[b]thiophene-2-il)carbonyl)-1-azabicycl[2,2,2]octane hydrochloride-1/5hydrate. Melting point: 236~238℃.

Example 18

[0058]

[CHEM. 26]



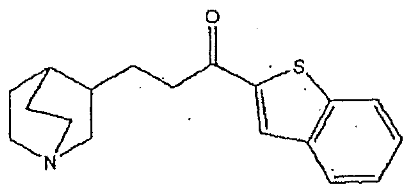
[0059] Using 1.0gr of

3-(3-(benzo[b]thiophene-2-il)-3-oxopropyl)-1-azabicyclo-[2,2,2]octane, similar reactions as in Example 8 were conducted to obtain 3-(3-(benzo[b]thiophene-2-il)propyl)-1-azabicyclo[2,2,2]-octane hydrochloride-1/4 hydrate. Melting point: 176~178℃.

Example 19

[0060]

[CHEM. 27]



[0061] Using 2.93gr of benzothiophene and 1.65gr of N-methyl-N-methoxy-3-(1-azabicyclo-[2,2,2]octane-3-il)propanamide, similar reactions as in Example 10 were conducted to obtain 1.6gr of 3-(3-(benzo[b]thiophene-2-il)-3-oxopropyl)-1-azabicycl[2,2,2]octane hydrochloride-1/5hydrate. Melting point: 280~282℃.

[0062] Preparation Formula Example 1

A well kneaded mixture of 0.5 part of the compound obtained in Example 1, 25 parts of lactose, 35 parts of crystalline cellulose and 3 parts of corn starch was well kneaded with a binder prepared from 2 parts of corn starch. The blend was passed through a 24 mesh sieve, was dried in an oven at 50℃, and was then passed through a 24 mesh sieve. Thus obtained kneaded powder was well blended with 8 parts of corn starch, 11 parts of crystalline cellulose and 9 parts of talc, and the blend was then compression-formed to tablets containing 0.5mg/tablet of the effective component.

[0063] Preparation Formula Example 2

Into water for injection, 1.0mg of the compound obtained in Example 1 and 9.0mg of sodium chloride were dissolved, pyrogens were removed by filtration, the filtrate was moved into ampul under antiseptic conditions, and the ampul was sterilized and melt sealed to obtain an injection preparation containing 1.0mg of the effective component.

[0064] Excellent pharmacological activities of compounds represented by the formula (I) are demonstrated in a series of tests as described below:

Experiment 1: Compatibility with $\alpha 7$ nicotinic receptors (bonding with $[^{125}I]$ α-bungarotoxin)

Rat's hippocampus was homogenized with the 15 times amount of a cooled 0.32M sugar solution, and was centrifugally separated at 1,000G for 10 minutes (4℃). The supernatant was recovered and subjected to centrifugal separation at 20,000G for 20 minutes (4℃), and precipitates were homogenized with cooled distilled water, and subjected to centrifugal separation at 8,000G for 20 minutes (4℃). After the supernatant was subjected to centrifugal separation at 40,000G for 20 minutes (4℃), pellets were homogenized again with cooled distilled water and subjected to centrifugal separation at 40,000G for 20 minutes (4℃). The final precipitates were stored in a refrigerator (−80℃). On the experimental day for bonding, the precipitates were suspended in a cooled buffer solution (comprising 118mM aqueous sodium chloride solution, 4.8mM aqueous potassium chloride solution, 2.5mM aqueous calcium chloride solution, 1.2mM aqueous magnesium sulfate solution and 20mM Na-HEPESS buffer pH7.5) to prepare a hippocampus membrane sample. According to the method in a prior report (Briggs CA et al., Functional characterization of the novel neural nicotinic acetylcholine receptor ligand GTS-21 in vitro and in vivo. *Pharmacolo. Biochem. Beehav.* 57 (1/2): 231-241, 1997), $[^{125}I]$ α

·bungarotoxin (>7.4TBq/mmol, IM·109, Amusham Inc.), the hippocampus membrane sample, a buffer solution (comprising 118mM aqueous sodium chloride solution, 4.8mM aqueous potassium chloride solution, 2.5mM aqueous calcium chloride solution, 1.2mM aqueous magnesium sulfate solution and 20mM Na·HEPESS buffer pH7.5), and a test compound were incubated at 37℃ for 3 hours. Quickly using a cell harvester (Brandale Inc.[sic]), the reaction was absorbed and filtered on a Whatman GF/B filter (pretreated for at least 3 hours, with an aqueous 0.5% polyethyleneimine solution containing 0.1& bovine serum albumin), and was washed three times with cooled buffer solutions. Radioactivity (^{125}I) bonded to the filter was counted with a gamma counter. Also, non·specific bonding was determined in the presence of 1 μM α·bungarotoxin (Wako Pure Chemical Industries, Co., Ltd.) or 100 μM (−)·nicotine (Research Biochemicals, Inc., USA). Specific bonding constituted 60~70% of the total bonding. Results from these experiments: IC_{50} values for compounds according to the present invention and control compounds are shown below: Compound numbers correspond to Example numbers. Control compounds A and B are as shown below:

Control A: AR·R 17779 (WO96/06098); and

Control B: 3·Benzyloxy·1·azabicyclo[2,2,2]octane (Compound 2 in Japanese Laid·Open Patent Application Hei·04 (1992)·226981A).

[0065]

[Table 1]

Compound numbers	Bonding with (^{125}I) α·bungarotoxin IC_{50} (nM)
1	59
3	26
5	150
7	26

8	65
9	22
10	150
11	130
12	170
13	70
15	97
16	110
Control A	680
Control B	3700

[0066] **Experiment 2**: Compatibility with $\alpha 4 \beta 2$ nicotinic receptors

(bonding with [^{3}H] Cylisine)

Rat's cerebral cortex was homogenized with the 15 times amount of a cooled 0.32M sugar solution, and was centrifugally separated at 1,000G for 10 minutes (4℃). The supernatant was recovered and subjected to centrifugal separation at 20,000G for 20 minutes (4℃), and precipitates were homogenized with cooled distilled water, and subjected to centrifugal separation at 8,000G for 20 minutes (4℃). After the supernatant was subjected to centrifugal separation at 40,000G for 20 minutes (4℃), pellets were homogenized again with cooled distilled water and subjected to centrifugal separation at 40,000G for 20 minutes (4℃). The final precipitates were stored in a refrigerator (−80℃). On the experimental day for bonding, the precipitates were suspended in a cooled buffer solution (comprising 120mM aqueous sodium chloride solution, 5mM aqueous potassium chloride solution, 2.5mM aqueous calcium chloride solution, 1mM aqueous magnesium sulfate solution and 50mM tris-hydrochloride acid buffer pH7.4) to prepare a cerebral cortex membrane sample.

[0067] [^{3}H] Cylisine (555GBq-1.48TBq/mmol, NET-1054, NEN Life Science Products, USA), the cerebral cortex membrane sample, a buffer solution (comprising 120mM aqueous sodium chloride solution, 5mM aqueous potassium chloride solution, 2.5mM aqueous calcium chloride solution,

1mM aqueous magnesium sulfate solution and 50mM tris-hydrochloric acid buffer pH7.4), and a test compound were incubated at 4℃ for 75 minutes. Quickly using a cell harvester (Brandale Inc.[sic]), the reaction was absorbed and filtered on a Whatman GF/B filter (pretreated for at least 3 hours, with an aqueous 0.5% polyethyleneimine solution containing 0.1% bovine serum albumin), and was washed three times with cooled buffer solutions. The filter was placed in a vial, and after the addition of a liquid scintillator, radioactivity (tritium) bonded to the filter was counted with a liquid scintillation counter. Also, non-specific bonding was determined in the presence of 10 μM (−)-nicotine (Research Biochemicals, Inc., USA). Specific bonding constituted 80% or more of the total bonding. As results from these experiments showed that compounds according to the present invention have an IC_{50} value of 1000nM or more and very poor compatibility with $\alpha 4 \beta 2$ nicotinic receptors. That is, compounds according to the present invention are compounds having selective compatibility with α nicotinic receptors.

[0068] Experiment 3: Agonist activity to α nicotinic receptors (Electro-physiological experiments with PC12 cells)

PC12 cells (acquired from Dainippon Pharmaceutical Co., Ltd.) were disseminated in a collagen-coated 35mm^2 culture plate, and after 1~3 day culture, the culture was electrophysiologically determined. According to a nystatine-drilling patch clamp method (refer to Akaike N, and Harata N., *Jap. J. Physiol.*, 44: 433-473, [1994]), under conditions where the membrane potential of PC12 cells were fixed (at VH=−70mV), a tested compound liquid (dissolved in a cell-external liquid) was administered according to a method for instantaneously exchanging the outside liquids (Y-tube method, refer to Murase et al., *Brain Res.* 525: 84-91 [1990]), and

the wavelength of a induced transient inward-directed current (a response to $\alpha 7$ receptors) was determined. The used cell-external liquid and pipet-internal liquid had the following compositions:

Cell-external liquid: comprised 135mM sodium chloride, 2mM potassium chloride, 1mM magnesium chloride, 5mM calcium chloride, 10mM glucose and 12mM HEPES, and having the pH value adjusted to 7.4 with tris-buffer.

Pipet-internal liquid: prepared by adding the 1/25 volume of a 1% nystatine-methanol solution to a solution comprising 150mM cesium chloride and 10mM HEPES and having the pH value adjusted to 7.2 with tris-buffer. The current response was analyzed by means of a software (pCLAMP software, ver.6, Axon Instruments), and the peak value of transient inward-directed currents via α nicotinic receptors was measured for every cell. For the relative comparison with control agents, response values for the experimental compounds are shown as percentages based on the value of 10mM response to chlorine as a agonist to all the $\alpha 7$ nicotinic receptors, which is shown as 100%. The result as shown in Figure 1 reveals that Compound 11 exhibited a partial agonist effect to $\alpha 7$ nicotinic receptors.

[0069]

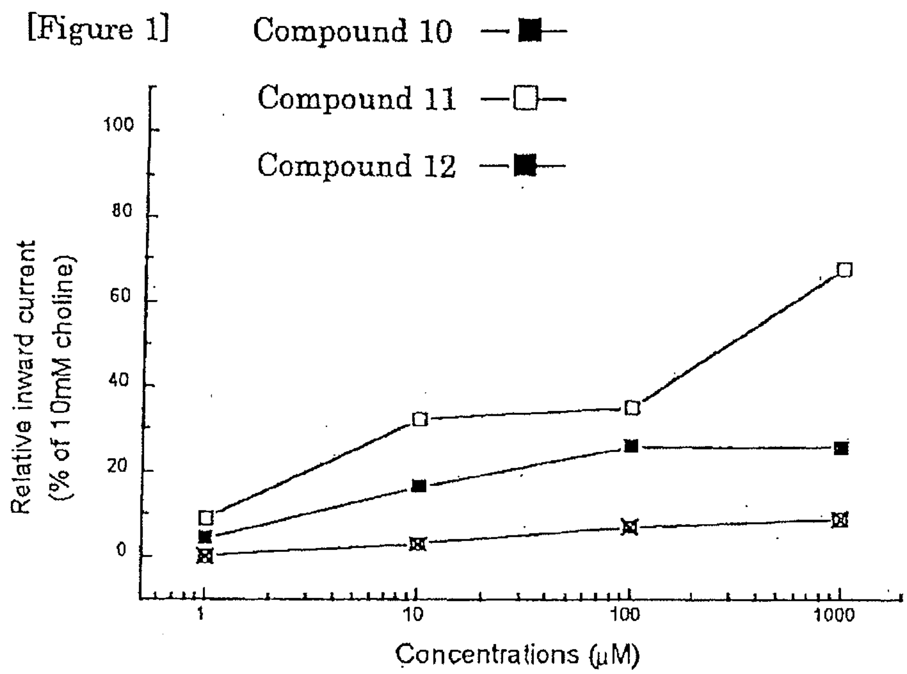
[Advantages of the Invention] Compounds represented by the formula (I), optical isomers thereof or pharmaceutically acceptable salts thereof have the selective and powerful action of effecting α-7 nicotinic receptors or effecting α-7 nicotinic receptor sections and are useful as a therapeutic or preventive agent for Alzheimer disease, cognitive function disorder, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pains, de la Tourette syndrome, Parkinson's disease, Huntington's

disease, etc., as a therapeutic or preventive agent for nervous degeneration diseases with the disorder of cholinergic neurotransmission, and moreover, as an agent for promoting the inhibition of smoking. Compounds according to the present invention also have excellent oral absorption and cerebral transition, and have favorable properties as a pharmaceutical for the central nervous system.

[Brief Explanation of Drawing]

Figure 1 shows results from Experiment 3.

[Figure 1]



[End]